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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/522,912	RIDDER ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-16 and 21-42* is/are pending in the application.

4a) Of the above claim(s) *21-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/28/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicants election with traverse of Group I is acknowledged. Applicant's election of enzyme label and antibody probe is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the restriction has been maintained. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 5, 17-20 and 43 have been canceled by Applicant. Claims 1-4, 6-16, 21-42 are pending in the application and Claims 21-42 have been withdrawn by Applicant. Claims 1-4, 6-16 are currently under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 2, 6-16 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claim 1 recites the limitations "at least one INK4a gene-product" and "at least one different INK4a gene product. Claim 1 further recites that the simultaneous

presence of cells overexpressing the one INK4a gene-product and cells expressing the one different INK4a gene product is indicative for neoplastic lesions. Claim 14 recites "wherein the probe is a polypeptide".

The specification discloses the INK4a gene-products p16 ^{INK4a} and p14 ARF (page 3, lines 26-30). Samples of neoplastic lesions were only examined for the presence of two INK4a gene products, p16 ^{INK4a} and p14 ARF (p43, lines 6-10).

The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as vertebrate "insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc.,358 F.3d 916 (Fed.Cir, 2004).

Thus, the instant specification may provide an adequate written description of INK4a gene products or polypeptide probes that are useful for discriminating metaplasias from neoplastic lesions, per Lilly by structurally describing a representative number of INK4a gene products that function as claimed or by describing structural features common to the members of the genus, which features constitute a substantial

portion of the genus. Further, the instant specification may provide an adequate written description of polypeptide probes by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the genus of INK4a gene products in a manner that satisfies the Lilly standard. There are insufficient structural features common to all members of the genus of INK4a gene products. The specification only discloses 2 INK4a gene products (page 3, lines 26-30. In fact, there are only two known INK4a gene products known (see Figure 1, Sherr, Nature Reviews Mol Cell Bio 2:731-737, 2001). The specification only describes the presence of the INK4a gene products, p16 ^{INK4a} and p14 ARF in neoplastic lesions (p43, lines 6-10). Thus, out of an undisclosed number of hypothetical INK4a gene products only two, p16 ^{INK4a} and p14 ARF were probed for and shown to be expressed in neoplastic lesions

Further, the specification only describes one polypeptide probe, an antibody (see example 5 and 6). Thus out of the multitude of members of the genus of polypeptides that includes antibodies, hormones, cytokines, peptidoglycans, G-proteins, lipoproteins, etc, only antibodies are described in the specification.

Thus the claimed peptides do not meet the standard set forth in Lilly.

The instant specification may also provide an adequate written description of the INK4a gene products if the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The specification only discloses two INK4a gene products, p16 ^{INK4a} and p14 ARF. These two INK4a gene products function as tumor suppressors (page 731, column 1 paragraph 1 to page 731, column 2, paragraph 2, Sherr, Nature Reviews Mol Cell Bio 2:731-737, 2001. However, these two INK4a gene products use different mechanisms to suppress cell growth (Id). Thus, although these two gene products share sequence homology the two INK4a gene products function in different ways to suppress cell growth. The specification is silent as to what sequences are sufficient to function as contemplated in the specification. Thus, the specification does not provide sufficient structural characteristics that correlate with the ability of the two INK4a gene products to function as contemplated by the specification and for the reasons set forth above do not meet the standards set forth by Enzo.

Further, the specification does not provide sufficient structural characteristics that correlate with the ability of the polypeptide probes to function as contemplated by the specification and for the reasons set forth above do not meet the standards set forth by Enzo.

Thus, the specification does not provide an adequate written description of the genus of INK4a gene products and polypeptide probes of claims 1, 2, 6-16 that is required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

3. Claims 1-4, 6-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Sano et al (Path Int 52:375-383, May 2002).

The claims are drawn to a method for discriminating metaplasia from neoplastic lesions comprising determining the presence of cells overexpressing at least one INK4a gene-product in a biological sample, determining the presence or absence of cells expressing at least one different INK4a gene-product in the biological sample, wherein the simultaneous presence of cells overexpressing the one INK4a gene product and cells expressing the one different INK4a gene-product is indicative for neoplastic lesions, wherein the INK4a gene product has a molecular weight between 13 and 19 kDa, wherein at least one INK4a gene-product is p16 ^{INK4a} and at least one different INK4a gene product is p14 ARF, wherein the neoplastic lesions is a lesion of the uterine cervix and the biological sample contains cells from the uterine cervix, wherein the biological sample is a cytological or histological preparation of he cervix uteri, wherein

the determination of the INK4a gene-products is performed using an enzyme-labeled antibody in an immuno-cytochemical staining procedure.

Sano et al (2002) disclose a method for determining the presence of the two INK4a gene products p16 ^{INK4a} and p14 ARF (molecular weights 16 kDa and 14 kDa, respectively) in cervical samples, taken from lesions of the uterine cervix, and found that both were expressed in carcinomas and displasia but not in condyloma acuminate or normal specimens (see Table 1). The uterine cervix is a part of the anogenital tract. Cervical specimens were immunohistochemically stained using antibodies to p16 ^{INK4a} and p14 ARF linked to the enzyme peroxidase (see Materials and Methods).

The following 35 U.S.C. 103(a) rejection is made in case the 35 U.S.C. 102(a) rejection above is overcome.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-4, 6-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sano et al (Am J Path 153:1741-1748, 1998) in view of O'Nions et al (Br J Cancer 85:1551-1556, Nov 2001).

The claims are described supra.

Sano et al (1998) teach a method for determining the presence of p16 ^{INK4a} in cervical samples and found strong and diffuse immunoreactivity for p16 ^{INK4a} in invasive cancer lesions but not in non-neoplastic tissues (see page 1745 column 1). Sano et al (1998) disclose that almost all preneoplastic and neoplastic lesions of the cervix are associated with human papilolomavirus (HPV) infection (see page 1741, 1st column 2nd paragraph). Furthermore, Sano et al (1998) disclose that HPV16 is associated with a high risk for neoplastic transformation (see page 1741, 2nd column 1st paragraph). Cervical specimens were immunohistochemically stained using antibodies to p16 ^{INK4a} and p14 ARF linked to the enzyme peroxidase (see Materials and Methods).

Sano et al (1998) does not specifically teach a method for determining the presence of p14ARF in cervical samples.

O'Nions teaches that p14 ARF RNA was over-expressed in the majority of vulva squamous cell cancers tested (see page 1555, 1st column, 1st paragraph). O'Nions disclose that HPV-positive cancers are associated with intraepithelial neoplasia (see page 1551, 1st column, 1st paragraph). Furthermore, 12 out of 13 vulva cancers associated with HPV16 infection over-expressed p14 ARF (see Table 1A). In addition 12 out of 13 vulva cancers associated with HPV16 infection over-expressed p16 ^{INK4a} (Id). All of the HPV associated vulva cancers over-expressed either p14 ARF and p16 ^{INK4a} (Id). The vulva is part of the anogenital tract.

One of ordinary skill in the art would have been motivated to apply O'Nions et al's teaching of over-expression of p14 ARF and p16 ^{INK4a} in HPV associated vulva cancer to Sano et al (1998) finding that p16 ^{INK4a} is over-expressed in cervical neoplasia because O'Nions et al discloses that vulva neoplasias are associated with HPV and both p14 ARF and p16 ^{INK4a} over-expressed in HPV-associated vulva cancer. It would have been prima facie obvious to one skilled in the art to have combined Sano et al's (1998) over-expression of p16 ^{INK4a} in HPV associated cervical neoplastic tissues with O'Nions et al's over-expression of p14 ARF and p16 ^{INK4a} in HPV associated vulva neoplasia.

Summary

5. No claim allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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